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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
YAEN, CHRISTOPHER H

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 02/12/2003 14

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/763,794	SIMON ET AL.	
	Examiner	Art Unit	
	Christopher H Yaen	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-59* is/are pending in the application.

4a) Of the above claim(s) *44-56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-43 and 57-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7 & 10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of group I in Paper No. 13 is acknowledged.

2. Claims 44-56 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 13. Applicant is reminded to cancel non-elected claims.

3. Therefore claims 34-43 and 57-59 are examined on the merits.

Information Disclosure Statement

4. The Information Disclosure Statements filed 7/12/01 and 8/9/01 (paper no. 7&10) is acknowledged and considered. A signed copy of the IDS is attached hereto.

5. It is noted that IDS A03 and A09 are foreign language documents of which there is no translation provided. These references are considered to the extent that they are present in the case, however, not translation was provided so as to determine if they represent prior art.

Claim Rejections - 35 USC § 112, 2nd paragraph

6. Claims 34-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Regarding claims 34-43, it is unclear from the preamble of claim 34 how concentration is to take place when the final result of the claim is the maturation of dendritic cells.

8. Regarding claim 34 and dependent claims thereof, it is not clear from the recited claims how mononuclear cells possessing CD14 are to be isolated, because the necessary steps are not clearly recited in the claims.

9. Regarding claim 35 in the recitation of the term "modified", it is not clear as to what types of modifications are to be included within the scope of the claims. How are the hyaluronic acid fragments to be modified.

10. Regarding claim 38 in the recitation of the phrase "at least one antibody", it is unclear as to what other antibody is to be encompassed, as such the metes and bounds of the term cannot be determined.

11. Regarding claim 58 in the recitation of the terms "peptide" and "antigen", it is unclear as to what types of antigens and peptides are to be considered part of the vaccine.

Claim Rejections - 35 USC § 112, 1st paragraph

12. Claims 34-43 and 57-59 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of concentrating dendritic cells and stimulating them and with fragments consisting of 2-12 hyaluronic acid basic building blocks and a medicament consisting of the dendritic cells isolated from the above method, does not reasonably provide enablement for a method or vaccine wherein the dendritic cells are stimulated with 1-50 hyaluronic building blocks. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or practice the invention commensurate in scope with these claims.

The claims of the instant invention are drawn to a process of concentrating and stimulating dendritic cells with hyaluronic acid fragment wherein there are from 1-50 basic building block of hyaluronic acid. The specification teaches that 2-12 basic building blocks seems to be the most effective in stimulating the differentiation of the dendritic cells, and that larger fragments such as 20-30 basic building blocks seem not to have any effect in stimulating dendritic cells (see page 14). The specification therefore teaches that the effect of dendritic cell maturation seems to be most effective when stimulated with smaller fragments. One of skill in the art would therefore find it difficult to practice the instant invention with fragments greater than 12 basic building blocks because it is not know from the teachings of the specification how basic building blocks greater than 12 are to be effective in stimulating dendritic cell maturation. One of skill in the art would be forced to determine how basic building blocks greater than 12 or larger fragments of hyaluronic acid are to be effective in stimulating dendritic cells. The working examples of the instant specification only teaches building blocks of 2-12 and that these are the most effective in eliciting the maturation of dendritic cells. There is no teaching provided in the specification in the form of working examples so as to guide one of skill in the art as to the effects or benefits of using fragments greater than 12 building blocks. As such one of skill in the art would be forced into undue experimentation to determine the benefits of using building blocks greater than 12. Therefore, the instant specification has only enabled one of skill in the art a process of maturing dendritic cells with hyaluronic acid basic building blocks of 2-12 in size.

Further, the claims are also drawn to a vaccine to be used as an immunomodulator. The term implies a prophylactic agent that is to be used to preemptively protect an individual from developing a certain disease. The specification has not taught to one of skill in the art how to prepare such a vaccine, who amongst the population would be good candidates for such a vaccine and the amounts and criteria for administration. As such, the specification has not enabled a vaccine to be used as an immunomodualtor, because it has not taught to one of skill in the art the necessary steps for preparation, the situations for use and the guidelines for administration.

Further still, it is not clear from the specification how matured dendritic cells that are to used as part of a vaccine are to uptake peptides. According to the specification, (see page 6), dendritic cells in immature status are only capable of taking up peptide antigens. Therefore, it is unclear as to how matured dendritic cells are to further contain peptide fragments or antigens for presentation, when they have already been matured through the use of low molecular weight hyaluronic acid fragments.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 34 and 59 are rejected under 35 U.S.C. 102(b) as being anticipated by Wenge *et al* (U.S. Patent 4725585, IDS A01). Claims are drawn to a process of concentrating dendritic cells or a process of maturing dendritic cells using hyaluronic

acid. Wenge *et al* teach a method of normalizing the phagocytic activity of granulocytes by using hyaluronic acid fragments. The claims of the instant invention are drawn to the same method because inherently, the hyaluonic acid fragments used by Wenge *et al* would also mature dendritic cells of the instant invention. Moreover, if the prior art structure is capable of performing the intended use, then it meets the claim. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

Claim Rejections - 35 USC § 102

15. Claim 57 is rejected under 35 U.S.C. 102(b) as being anticipated by Noble *et al* (1998, IDS A12). Claim is drawn to a vaccine comprising dendritic cells that have been matured by hyaluronic acid fragments. Nobel *et al* anticipates the instant claims because the hyaluronic acid fragments inherently mature dendritic cells and the intended use of the product does not carry any patentable weight. If the structure is able to perform in the same function as that previously described in the art, then it reads on the prior art.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

18. Claims 34-43 and 57-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brand *et al* (Eur. J. Immunol. 1998 May;28(5):1673-1680) in view of Noble P *et al* (1998, IDS A12). Claims are drawn to a process of concentrating dendritic cells (DC) comprising the steps of adding low molecular weight hyaluronic acid fragments to the DC. The claims are also drawn to a vaccine consisting of DC derived from the process of developing the as described above.

Brand *et al* disclose the role of extracellular matrix proteins on the maturation of DC. Brand *et al* further discloses the general process of isolating CD14 positive mononuclear cells through density gradients and antibody selection of CD14 positive mononuclear cells. Brand *et al* however fails to disclose the use of hyaluronic acid fragments as a source of stimulating DC.

Noble P *et al* however do disclose the role of the extracellular matrix protein hyaluronan and the role smaller fragments of this protein play in stimulating macrophage gene expression.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use small molecular weight fragments of hyaluronic acid for the stimulation of CD14 positive mononuclear cells resulting in the maturation of

mature dendritic cells. One of ordinary skill in the art would have been motivated to combine the references to practice the instant invention because the role of the extracellular matrix in stimulating mononuclear cell development was already known and practiced according to the teachings of Brand *et al*, wherein they disclose the techniques used by the instant invention to isolate and concentrate CD14 positive mononuclear cells and further show how extracellular proteins, such as fibronectin and collagen, induce the production of TNF-alpha. Furthermore, Nobel P *et al* teach that hyaluronan fragments of small molecular weight play a significant role in stimulating gene expression in inflammatory cells wherein there is an increase in stimulatory cytokines, such as TNF-alpha. One of skill in the art would have therefore been motivated to combine because both show that extracellular matrix proteins are able to elicit or induce the production of TNF-alpha in inflammatory cells, and that both are able to induce the maturation of the stem cells into differentiated mature immune effector cells. One of skill in the art would have expected a reasonsalbe amount of success in attempting the instant methods because the art teaches all the limitations of the invention. Although not explicitly stated, one of ordinary skill in the art would have found it obvious to use the maturated dendritic cells as vaccines in the treatment of disease.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H Yaen whose telephone number is 703-305-3586. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Christopher Yaen
Art Unit 1642
February 10, 2003

ALI R. SALIMI
PRIMARY EXAMINER